Oligometastatic lung cancer - a different entity with different treatment approaches?

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A different lung cancer entity with different treatment approaches?

Since the concept of oligometastatic state has been described in 1995,[1] the interest in the heterogeneity of stage IV non-small cell lung cancer (NSCLC) has exponentially grown. To date, the correct definition of oligometastatic disease is still under debate as it describes a subset of patients with a more favorable disease compared to the counterpart with bulky diffusion of metastasis. In fact, up to 86 % 5-year survival rate has been reported[2] for radical treatment of solitary metastasis while the general 5-year overall survival (OS) rate of stage IV NSCLC is less than 10 %.[3]

Definition of oligometastatic state

A homogeneous definition of this state is mandatory when a radical treatment is technically feasible for all tumor sites and may modify the disease course leading to long-term survival.[4] Recently a pan-European multidisciplinary consensus group established the criteria for synchronous oligometastatic disease definition, indicating a maximum of 5 metastases in no more than 3 organs.[4] Positron emission tomography (PET-CT) has been considered mandatory for mediastinal staging (Fig. 1), even though not sufficient in all cases.

Treatment options

The mainstay of stage IV lung cancer remains the platinum-based palliative chemotherapy, with additional therapeutic options being targeted therapies with alkaline phosphatase (ALK) or epidermal growth factor receptor (EGFR) inhibitors, and a number of immune-checkpoint inhibitors. However, the recent improvements in surgery and radiotherapy have imposed the role of the local ablative treatments in the multi-modality approach for the oligometastatic disease.

A provocative phase II trial conducted by Gomez et al. in 2016[5] was terminated early after the interim analysis showed significantly better results in the interventional arm. The trial enrolled patients for local consolidative treatment (LCT) including chemo-radiotherapy (CRT), radiotherapy or resection vs. maintenance chemotherapy alone. At 12,4 months of follow-up the progression-free survival (PFS) was 11,9 for the interventional group and 3,9 months for the standard of care with an odds ratio (OR) of 0,35. A number of small prospective and retrospective studies also suggest that radical local therapies provide good results in long-term disease control.[5–12]

The role of surgery

As regards the best treatment for the primary site, large epidemiological databases analyses have been recently published. The first one,[13] based on data extracted from the National Cancer Database, considered a population of over 3000 patients who underwent lung resection for stage IV NSCLC. It reported a 5-year OS of 21,1 %, recommending surgical resection for tumors staged T1-2,N0-1,M1 or T3N0M1. In this series, information on metastasis treatment was not provided, drawing only partial conclusions on definitive treatment. The second large population-based study was based on the Surveillance, Epidemiology and End Results database.[14] This retrospective analysis was conducted on over 39 000 cases of stage IV NSCLC, of which 1206 underwent surgical resection of primary tumor. The authors found that primary tumor resection was associated with significantly longer OS in different cohorts of patients. Other clinical studies favored surgery for the primary site as cornerstone treatment of oligometastatic NSCLC. As an example, the paper of Griffioen[9] showed that, in a context of radical treatment, lung resections patients have better prognosis in terms of OS, PFS and survival after the first progression. These results were confirmed by Xu[15], who reported that primary tumor excision conditioned the prognosis in patients with synchronous solitary metastasis.

The surgical resection of the metastatic sites has been reported to improve the outcome. Congedo[16], analyzing their long-term results, found that the complete control of the metastatic lesion by surgery (more than with radiation or chemotherapy), had a beneficial impact on the disease-free survival (DFS). Overall, the paradigm of surgical strategy for metastasis treatment started with the management of brain lesions and was extended to multiple organs with good results.[17] Xu[15] reported better results with the use of surgery or radiosurgery in the treatment of brain and adrenal metastasis, compared with those who did not receive it, while this difference was not observed for bone lesions. They concluded that even in case of unusual metastatic site aggressive treatments including surgery should be considered.

Although surgery seems to provide the best results, there is a potential selection bias favoring the outcomes. Surgical candidates have usually a good performance status, less medical comorbidities and lower burden of thoracic disease. Looking at the metastatic sites, many patients might present non-resectable deposits, as in most case of bone lesions, or being precluded from surgery for high surgical risk.

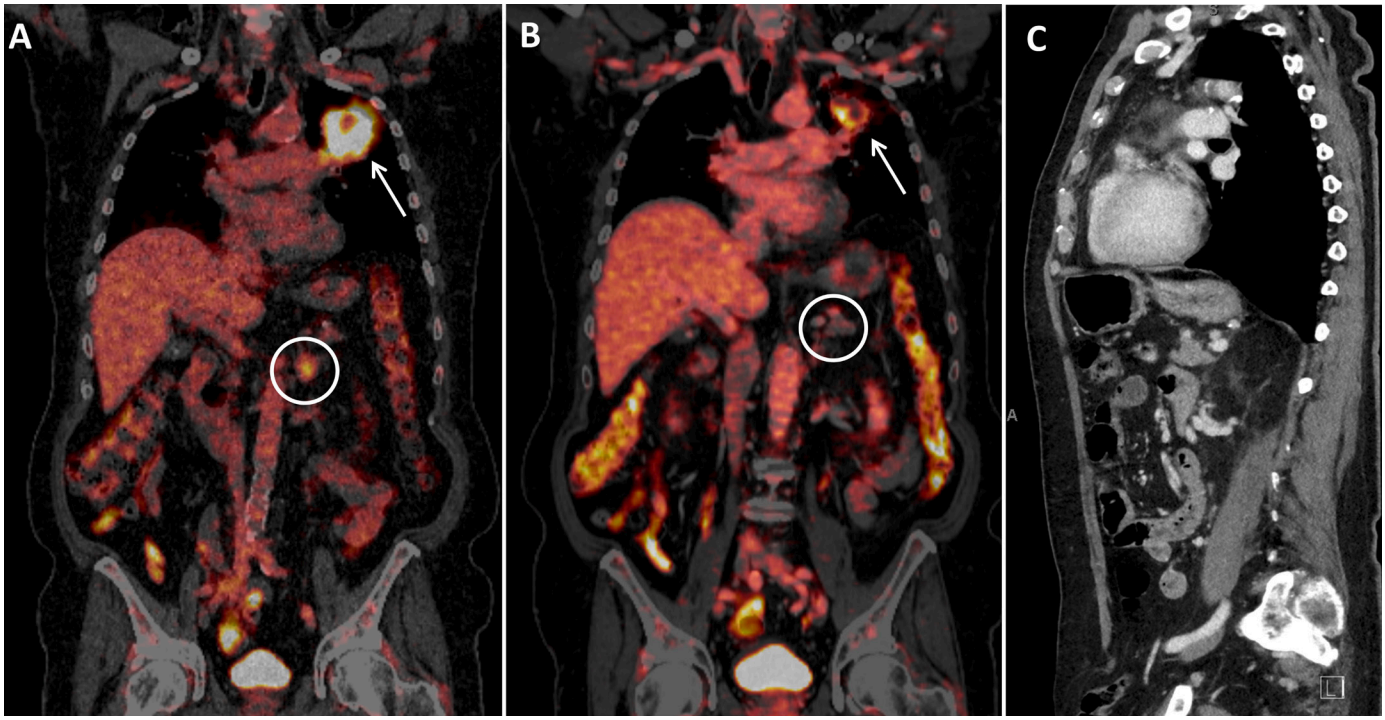

Fig. 1: 64-year-old patient with adenocarcinoma of the left upper lobe (white arrow) and left adrenal metastasis (white circle). A: PET scan at first diagnosis. B: Re-staging after induction therapy (3 cycles of chemo-immunotherapy with carboplatin, pemetrexed and pembrolizumab). C: No evidence of recurrent disease after one year from left upper lobectomy and left laparoscopic adrenalectomy

A recent meta-analysis on the evolution of treatment strategies in oligometastatic NSCLC[18] evidenced a considerable change in the management over the past 20 years. Initial treatment of choice for metastasis was surgery, while after 2011 (SBRT era), there has been an increased use of radiotherapy, mostly in the form of SBRT and no difference in OS was observed between surgery and radiotherapy studies. These results may reflect the evolution in radiotherapy strategies with the ability to deliver potentially ablative doses to different sites throughout the body, allowing curative treatments for unresectable metastasis.[19]

Prognostic factors

Accurate patient's selection remains crucial for obtaining the best results when choosing a radical treatment. Different factors have been investigated for possible association with prognosis, with the aim to select upfront the best candidates for aggressive therapies. Sex, age, nodal status, performance status, intrathoracic stage, smoking status and histology have been the most advocated prognostic factors. In a meta-analysis published by Shi and colleagues[20], the nodal status was significantly related with the OS. These results are in line with most published reports, either from clinical series or analysis of epidemiological databases.[15–18, 21–24] In this light, a complete nodal staging before radical treatment is highly recommended.[4,20] Other studies reported that age and performance status influence the prognosis of these patients. Ampil[25], in a series of 72 cases, found that patients with solitary metastasis younger than 65 years had a longer survival compared to the older counterpart. It is intuitive that patients in better general conditions are more prone to be included in aggressive treatment programs. As an example, the study of Frost[26] analyzed 107 patients who received local ablative treatments for synchronous single organ metastatic lung cancer, comparing them with 266 patients who did receive palliative treatments. Good performance status was strongly associated with better survival within the control group and remained associated with good outcome after propensity score matching of groups. The published literature generally indicates that patients in good clinical conditions could be possibly selected for upfront aggressive treatments and for further therapies after first progression.

Future perspectives

Finally, a mention on the role of the multimodality approach is mandatory. Usually the literature supporting the use of systemic therapies involves patients with widespread metastatic tumors rather than with limited disease. However, a combined effect of immunotherapy and local ablative therapies has been observed in NSCLC, with benefits in disease control.[6,10] The use of induction systemic therapy may serve as selection criteria for patients who might experience long-term PFS with additional local ablative treatments. In the era of immunotherapy, combined treatments and the fascinating "abscopal effect" with the combined use of immunotherapy and radiotherapy has been suggested.[27]

Take-home message

In conclusion, the oligometastatic NSCLC represents a subset of stage IV lung cancer with a different biological behavior that may benefit from aggressive local treatments in a context of multimodality approach. Current evidences push towards surgical resection of the primary tumor for selected patients along with surgical and/or radiation therapy for all metastatic sites combined with systemic therapy. Herein the addition of immunotherapy seems to be very promising. More studies are needed to better understand the tumor

biology, to tailor well-balanced treatments and to better select the patients. ■

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NEWS

Krebsliga Schweiz würdigt Engagement

Dieses Jahr verleiht die Krebsliga Schweiz zwei Anerkennungspreise: einen an das mobile Palliative-Care-Team Voltigo in Freiburg und einen an die Schweizerische Gesellschaft für Psychoonkologie (SGPO). Ausserdem erhält Altbundesrätin Ruth Dreifuss die Krebsmedaille für ihr Engagement für bezahlbare Medikamente und die Zugangsgerechtigkeit in der medizinischen Versorgung.

Mit dem mit 5000 Franken dotierten Anerkennungspreis zeichnet die Krebsliga Schweiz Personen und Organisationen aus, die die Situation von Krebsbetroffenen verbessern. Dieses Jahr verleiht die Krebsliga den Preis gleich zwei Mal: an das mobile Palliative-Care-Team Voltigo in Freiburg sowie an die SGPO.

Im Kanton Freiburg können an Krebs erkrankte Menschen und ihre Angehörigen seit zehn Jahren auf Voltigo zählen. Das mobile Palliative-Care-Team lindert die Leiden und pflegt die Kranken am Ort ihrer Wahl, auch bei ihnen zu Hause. Damit trägt es massgeblich zur bestmöglichen Lebensqualität der Betroffenen bei. Die SGPO wurde 2003 gegründet und hat die psychosoziale Begleitung und Betreuung von Krebsbetroffenen und ihren Angehörigen institutionalisiert und professionalisiert. Dadurch wurde ein wichtiger Beitrag zur Verbesserung von psychosozialen Unterstützungsdiensten geleistet.

Einsatz für mehr Zugangsgerechtigkeit

Mit der Krebsmedaille würdigt die Krebsliga Schweiz aussergewöhnliche Verdienste im Kampf gegen Krebserkrankungen und ihre Folgen. Die diesjährige Medaille geht an Altbundesrätin Ruth Dreifuss. Sie hat sich während – aber auch nach – ihrer Amtszeit sehr für bezahlbare Medikamente und die Zugangsgerechtigkeit in der medizinischen Versorgung eingesetzt. *(red)* ■

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